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WO 01/87343 A2

(54) Title: COMBINATION THERAPY USING COX-2 SELECTIVE INHIBITOR AND THROMBOXANE INHIBITOR AND COMPOSITIONS THEREFOR

(57) Abstract: The present invention provides a method for the treatment or prophylaxis of COX-2 mediated conditions in patients who are at risk of developing thromboembolic events which comprises administering to said patient a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor and a cardiovascular protective amount of a thromboxane inhibitor, as well as compositions therefor.

TITLE OF THE INVENTION

COMBINATION THERAPY USING COX-2 SELECTIVE INHIBITOR AND THROMBOXANE INHIBITOR AND COMPOSITIONS THEREFOR

BACKGROUND OF THE INVENTION

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme. More recently a second, inducible, form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been identified. COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors.

COX-1 is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, COX-2 is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Most traditional NSAIDs inhibit both COX-1 and COX-2 isoforms of cyclooxygenase, and therefore their desirable antiinflammatory effect is often accompanied by undesirable gastrointestinal damaging effect. Selective inhibitors of COX-2 have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug but have a diminished ability to induce some of the mechanism-based side effects. COX-2 selective inhibitors currently on the market, rofecoxib and celecoxib, have been shown to have much lower incidence of gastrointestinal side effects than traditional NSAIDs (NSAIDs that have no or little selectivity for COX-2 over COX-1).

Traditional NSAIDs also affect platelet function by virtue of their COX-1 inhibitory activity. Inhibition of COX-1 prevents the formation in platelet of thromboxane A2, a mediator that promotes platelet aggregation. This effect of NSAIDs on platelet function has been exploited therapeutically, as in the case of aspirin, in the prophylaxis of thromboembolic disorders. COX-2 inhibitors, on the other hand, are not expected to have such protective effect.

In patients who are taking COX-2 selective inhibitors, those who are at risk of developing thromboembolic event may benefit from the anti-platelet aggregation effect of traditional NSAIDs, such as aspirin. However, the chronic use of aspirin for its cardiovascular protective effect, albeit at doses lower than normally used for its antiinflammatory effect, would undesirably expose these patients to gastrointestinal side effects while they are on an otherwise GI-sparing treatment regimen. Therefore, for patients who are taking COX-2 selective inhibitors and who may benefit from the cardiovascular protective effect of aspirin, there remains a need for a cardiovascular protective treatment that does not expose them to increased risk for gastrointestinal side effects.

PCT Published Application WO00/18352 discloses a method for treating inflammtory diseases by administering a thrombin inhibitor, which may be used in combination of an NSAID, such as COX-2 inhibitors.

PCT Published Application WO99/45913 discloses combination therapy and composition for acute coronary ischemic syndrome using an antiplatelet agent and a COX-2 inhibitor.

SUMMARY OF THE INVENTION

The present invention concerns a method for treating patients with COX-2-mediated conditions, and who are also at risk of developing thromboembolic events which comprises administering to said patients a COX-2 selective inhibitor and a thromboxane A2 inhibitor. Also provided are pharmaceutical compositions comprising a COX-2 selective inhibitor and a thromboxane inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel method for the treatment or prophylaxis of COX-2-mediated conditions in patients who are at risk of developing thromboembolic events which comprises administering to said patients a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor and a cardiovascular protective amount of a thromboxane inhibitor.

The present invention also provides for pharmaceutical compositions comprising a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor and a cardiovascular protective amount of a thromboxane inhibitor, and a pharmaceutically acceptable carrier in unit dosage form.

The present invention also provides a pharmaceutical product comprising (1) a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor in a first oral unit dosage form, (2) a cardioprotective amount of a thromboxane inhibitor in a second oral unit dosage form, and (3) instructions for concurrent or sequential administration of said pharmaceutical product to a patient in need thereof.

In one embodiment of the present method, the COX-2 mediated condition is selected from osteoarthritis, rheumatoid arthritis, cancer and Alzheimer's disease. In one subset the COX-2 mediated condition is cancer. In another subset the COX-2 mediated condition is Alzheimer's disease; in yet another subset, the COX-2 mediated condition is osteoarthritis or rheumatoid arthritis.

In another embodiment the COX-2 selective inhibitor and the thromboxane inhibitor are administered orally.

In another embodiment the COX-2 selective inhibitor is selected from celecoxib, rofecoxib, valdecoxib and etoricoxib.

"Conditions mediated by COX-2" include, but are not limited to, pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures, cancer including the transformation of a colonic adenoma to a colonic adenocarcinoma, and dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease (ie Alzheimer's dementia).

"Thromboembolic event" includes, but are not limited to, ischemic stroke, transient ischemic stroke, and myocardial infarction. "Patients who are at risk of developing thromboembolic events" include those with a familial history of, or genetically predisposed to, thromboembolic disorders, who have had ischemic stroke, transient ischemic stroke, myocardial infarction, and those with unstable angina pectoris or chronic stable angina pectoris and patients with altered prostacyclin / thromboxane A_2 homeostasis or higher than normal thromboxane A_2 levels leading to increase risk for thromboembolism, including patients with diabetes and rheumatoid arthritis.

"COX-2 selective inhibitors" embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. COX-2 and COX-1 inhibitory activities may be determined employing the human whole blood COX-1 assay and the human whole blood COX-2 assay described in C. Brideau *et al, Inflamm. Res. 45*: 68-74 (1996), herein incorporated by reference. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 2 μM in the human whole blood COX-2 assay, yet have a cyclooxygenase-1 IC_{50} of greater than about 5 μM in the human whole blood COX-1 assay. Also preferably, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 5, and more preferably of at least 30.

"Thromboxane inhibitors" include compounds that inhibit thromboxane synthase and compounds that inhibit, prevent or otherwise interfere with the binding of thromboxane to its receptor (thromboxane antagonists), as well as compounds that are both thromboxane synthase inhibitors and thromboxane receptor antagonists. Thromboxane synthase inhibitors and thromboxane receptor antagonists can be identified using assays described in Tai, H.-H. Assay of thromboxane A synthase inhibitors. Methods in Enzymology Vol 86, 1982 pp. 110-113 and references contained within Hall, S. E. Thromboxane A_2 Receptor Antagonists. Medicinal Research Reviews, 11, 503-579 (1991) and Coleman, R. A., Smith, W. L., Narumiya, S. International Union of Pharmacology classification of prostanoid receptors: properties, distribution and structure of the receptors and their subtypes. Pharmacol. Rev. 46, 205-229 (1994). The characteristics of the preferred thromboxane inhibitor should include suppression of thromboxane A_2 formation (thromboxane synthase inhibitors) and/or blockade of thromboxane A_2 and prostaglandin H_2 on platelets and vessel wall (thromboxane receptor antagonists). The effects should block platelet activation and therefore platelet function. Thromboxane synthase inhibitors may also increase the synthesis of antiaggregatory prostaglandins including prostacyclin and prostaglandin D_2.

"Therapeutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treatment" or "treating" includes alleviating, ameliorating, relieving or otherwise reducing the signs and symptoms associated with a disease or disorder.

The term "prophylaxis" means preventing or delaying the onset or the progression of a disease or disorder, or the signs and symptoms associated with such disease or disorder.

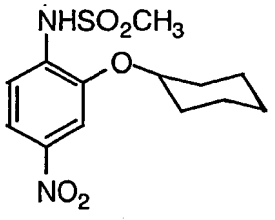
"Prophylactically effective amount" means that amount of a pharmaceutical drug that will prevent, delay or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

"Cardiovascular protective amount" means that amount of a thromboxane inhibitor that will prevent or reduce the risk of occurrence of thromboembolic events.

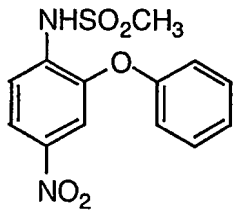
The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a COX-2 selective inhibitor and a thromboxane inhibitor, and pharmaceutically acceptable excipients.

COX-2 Selective Inhibitors

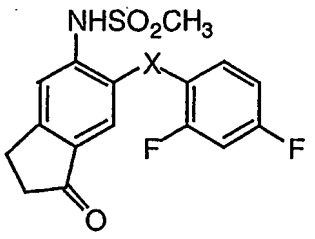
As explained in J. Talley, *Exp. Opin. Ther. Patents* (1997), 7(1), pp. 55-62, three distinct structural classes of selective COX-2 inhibitor compounds have been identified. One class is the methane sulfonanilide class of inhibitors, of which NS-398, flosulide, nimesulide and (i) are example members.



NS-398

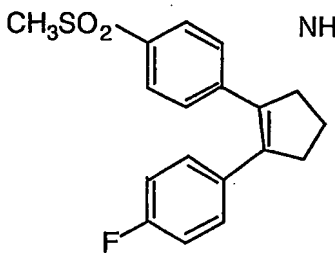


Nimesulide

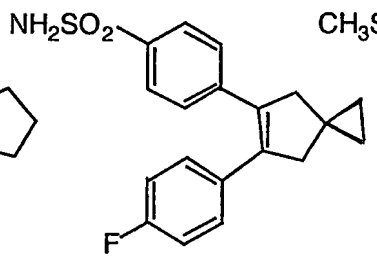


(i), X = S
Flosulide, X = O

A second class is the tricyclic inhibitor class, which can be further divided into the sub-classes of tricyclic inhibitors with a central carbocyclic ring (examples include SC-57666, 1, and 2); those with a central monocyclic heterocyclic ring (examples include DuP 697, SC-58125, SC-58635, and 3, 4 and 5; and those with a central bicyclic heterocyclic ring (examples include 6, 7, 8, 9 and 10). Compounds 3, 4 and 5 are described in U.S. Patent No. 5,474,995.



SC-57666



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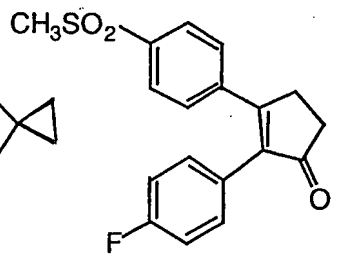

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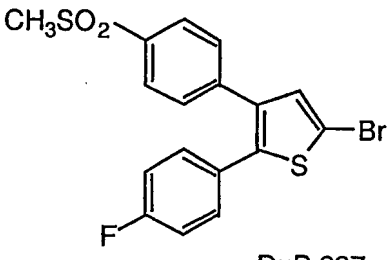
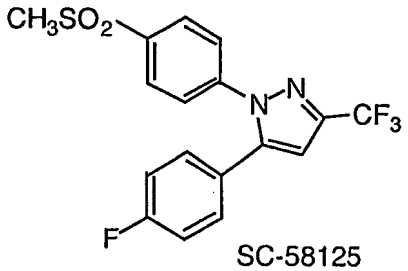
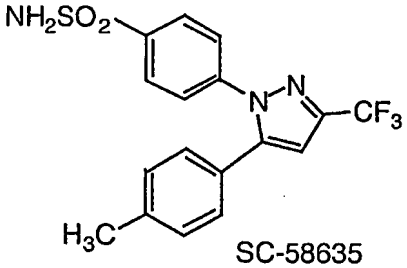


DuP 697



SC-58125



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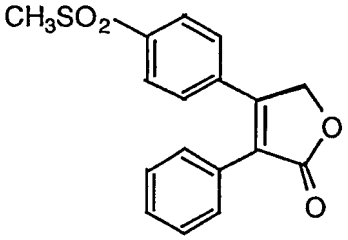

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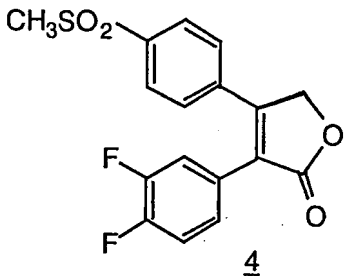

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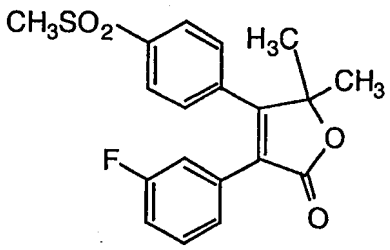

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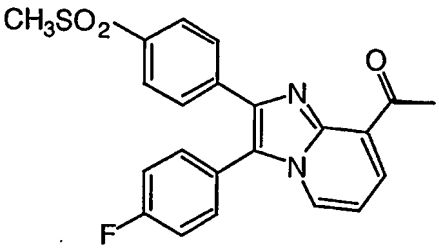

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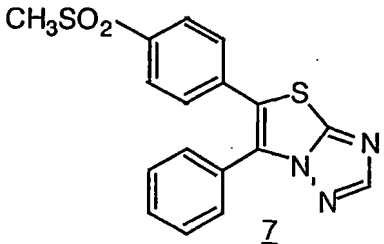

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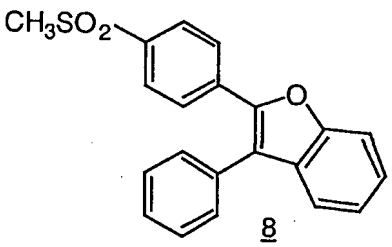

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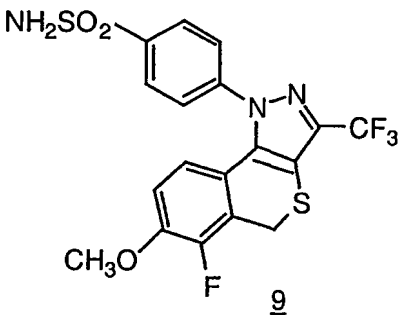

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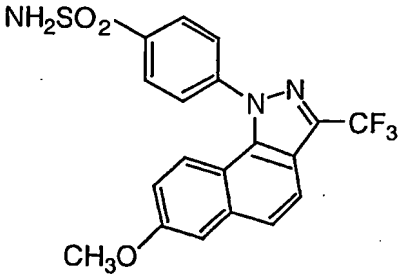

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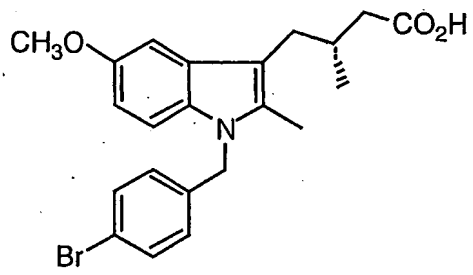
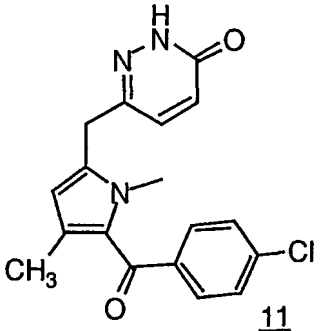
The third identified class can be referred to as those which are structurally modified NSAIDs, and includes 11a and structure 11 as example members.



11a



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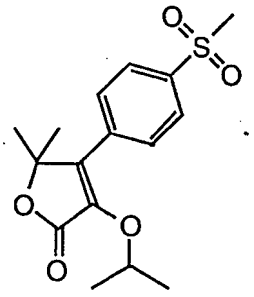
In addition to the structural classes, sub-classes, specific COX-2 selective inhibitor compound examples, and reference journal and patent publications described in the Talley publication which are all herein incorporated by reference, examples of compounds which selectively inhibit cyclooxygenase-2 have also been described in the following patent publications, all of which are herein incorporated by reference: U.S. Patent No.'s 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752, 5,550,142, 5,552,422, 5,604,253, 5,604,260, 5,639,780; and International Patent Specification Nos. 94/13635, 94/15932, 94/20480, 94/26731, 94/27980, 95/00501, 95/15316, 96/03387, 96/03388, 96/06840; and International Publication Nos. WO 94/20480, WO 96/21667, WO 96/31509, WO 96/36623, WO 97/14691, WO 97/16435.

Additional COX-2 selective inhibitor compounds which are included in the scope of this invention include:



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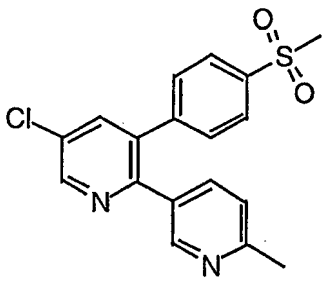

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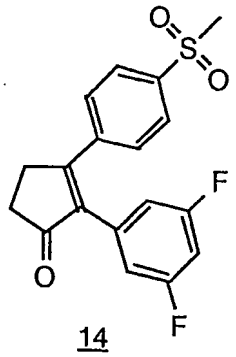

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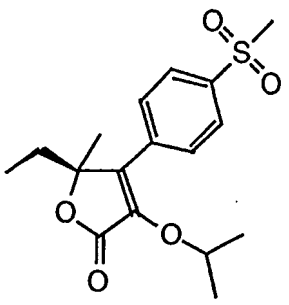

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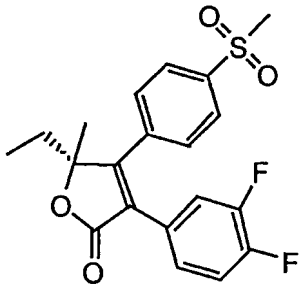

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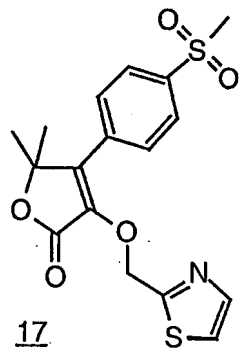

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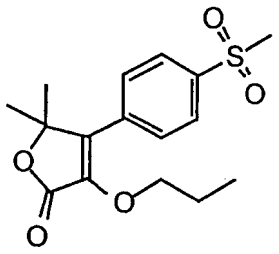

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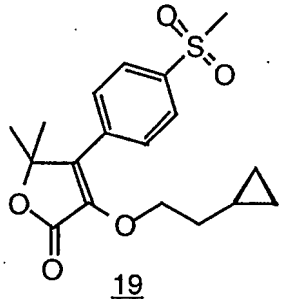

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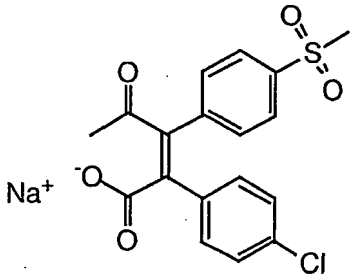

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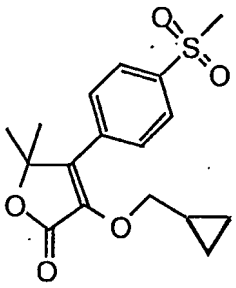

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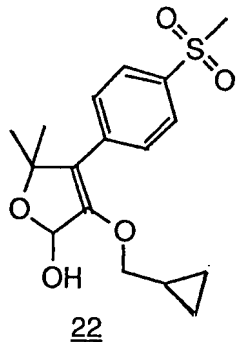

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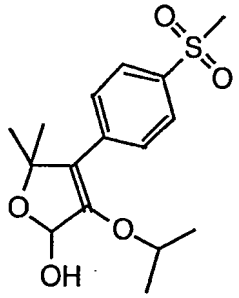

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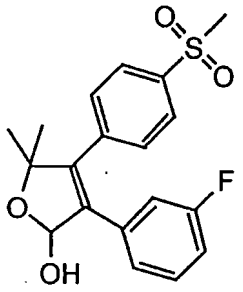

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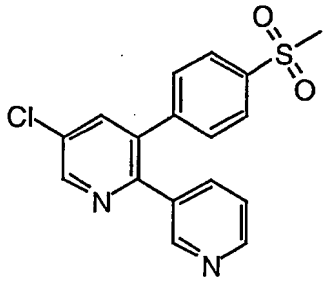

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Some of the compounds above can also be identified by the following chemical names:

SC58635: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene-sulfonamide (celecoxib);

3: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone (rofecoxib);

4: 3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;

5: 5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(3-fluorophenyl)-5H-furan-2-one;

12: 5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

13: 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine (etoricoxib);

14: 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

15: 5(S)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

16: 5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(3,4-difluorophenyl)-5H-furan-2-one;

17: 3-((2-thiazolyl)methoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

18: 3-propyloxy-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

19: 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

20: sodium 2-(4-chlorophenyl)-3-(4-(methylsulfonyl)phenyl)-4-oxo-2-pentenoate;

21: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

22: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydro-furan-2-ol;

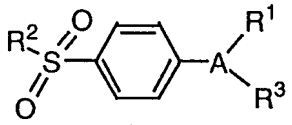
23: 3-isopropoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol

24: 5,5-dimethyl-3-(3-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran

25: 5-Chloro-3-(4-(methylsulfonyl)phenyl)-2-(3-pyridinyl)pyridine

The following publications describe and/or provide methods for making the compounds as indicated: compounds 12, 15, 17, 18, 19 and 21, WO 97/14691; compounds 22, 23 and 24, WO 97/16435; compound 20, WO 96/36623; compound 14, U.S. Patent No. 5,536,752; compound 16, U.S. Patent No. 5,474,995. See Examples herein for compounds 13 and 25

Also incorporated herein by reference are those compounds described in WO 96/41645 as having structural Formula I, shown below, and the definition and preferred definitions and species described therein:



I

Particularly preferred compounds of formula (I) include:

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)-pyrazole;

4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(4-chloro-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-chlorophenyl)-3-(hydroxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
5-(4-fluorophenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
4-(6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl)benzenesulfonamide;
6-(4-fluorophenyl)-7-(4-(methylsulfonyl)phenyl)spiro[3.4]oct-6-ene;
5-(3-chloro-4-methoxyphenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
4-(6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl)benzenesulfonamide;
5-(3,5-dichloro-4-methoxyphenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
5-(3-chloro-4-fluorophenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
4-(6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl)benzenesulfonamide;
2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)-phenyl)thiazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
1-methylsulfonyl-4-(1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl)-benzene;
4-(4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl)benzenesulfonamide;
5-(4-fluorophenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hepta-4,6-diene;
4-(6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl)benzenesulfonamide;
6-(4-fluorophenyl)-2-methoxy-5-(4-(methylsulfonyl)phenyl)-pyridine-3-carbonitrile;
2-bromo-6-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-pyridine-3-carbonitrile;
6-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-2-phenyl-pyridine-3-carbonitrile;
4-(2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfon-amide;
4-(2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfon-amide;
4-(2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfon-amide;
3-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzenesulfon-amide;
2-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridine;
2-methyl-4-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-pyridine;
2-methyl-6-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-pyridine;
4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzene-sulfonamide;
2-(3,4-difluorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

2-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-methyl-1H-imidazole;
2-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-phenyl-1H-imidazole;
2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-imidazole;
2-(3-fluoro-4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
1-(4-(methylsulfonyl)phenyl)-2-phenyl-4-trifluoromethyl-1H-imidazole;
2-(4-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-trifluoromethyl-1H-imidazole;
4-(2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
2-(3-fluoro-5-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
2-(3-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(3-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
1-(4-(methylsulfonyl)phenyl)-2-(3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
4-(2-phenyl-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
4-(2-(4-methoxy-3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
1-allyl-4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazole;
4-(1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl)benzenesulfonamide;
N-phenyl-(4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
ethyl (4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetate;
4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-1-(2-phenylethyl)-1H-pyrazole;
4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
1-ethyl-4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazole;
5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(trifluoromethyl)-1H-imidazole;
4-(4-(methylsulfonyl)phenyl)-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

5-(4-fluorophenyl)-2-methoxy-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)-pyridine;
2-ethoxy-5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)-pyridine;
5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
2-bromo-5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)-pyridine;
4-(2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl)benzenesulfonamide;
1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)benzene;
5-difluoromethyl-4-(4-(methylsulfonyl)phenyl)-3-phenylisoxazole;
4-(3-ethyl-5-phenylisoxazol-4-yl)benzenesulfonamide;
4-(5-difluoromethyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-(5-hydroxymethyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (valdecoxib);
N-propanoyl-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
1-(2-(4-fluorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-chlorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(2,4-dichlorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-trifluoromethylphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-methylthiophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl)benzenesulfonamide;
1-(2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl)benzenesulfonamide;
4-(2-(4-fluorophenyl)cyclopenten-1-yl)benzenesulfonamide;
4-(2-(4-chlorophenyl)cyclopenten-1-yl)benzenesulfonamide;
1-(2-(4-methoxyphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(2,3-difluorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl)benzenesulfonamide;
1-(2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)benzenesulfonamide;
4-(2-(2-methylpyridin-5-yl)cyclopenten-1-yl)benzenesulfonamide;

ethyl 2-(4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazol-2-yl)-2-benzyl-acetate;

2-(4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazol-2-yl)acetic acid;

2-(tert-butyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazole;

4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-2-phenyloxazole;

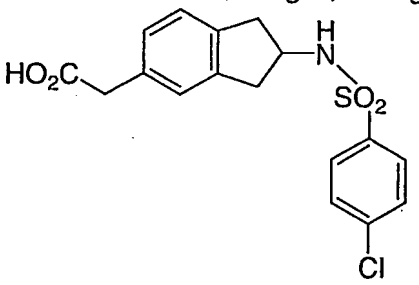
4-(4-fluorophenyl)-2-methyl-5-(4-(methylsulfonyl)phenyl)oxazole; and

4-(5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl)benzenesulfonamide; or a pharmaceutically acceptable salt thereof.

Several of the above mentioned COX-2 selective inhibitors have been approved for human use or are in advanced stage of development; accordingly, one subset of COX-2 selective inhibitors of the present invention include celecoxib, rofecoxib, valdecoxib and etoricoxib.

Thromboxane Inhibitors

Examples of thromboxane inhibitors include serabenast (seratrodast), picotamide, ozagrel, egualen, domitroban, ramatroban, ridrogrel, samixogrel, terbogrel, satrigrel, sulotraban, ifetroban, vapiprost, daltroban, imitrodast, dazoxiben, linotroban, triletide, nafagrel, rolafagrel, pirmagrel,



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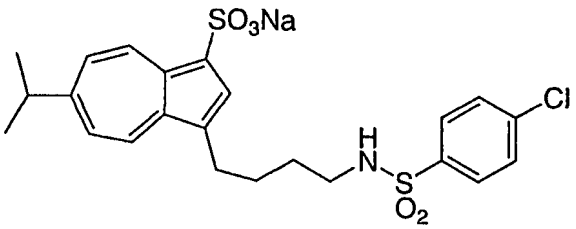

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S18886, S32080, ICI192605, ICI185282, ONO-3708, ONO-8809, FPL-55712, WHR-2348, KW3635, LCB2853, Y20811, CGS12970, CGS22652, UK34787, MED27, ONO1301, MR948, AZ1355, KD1792 and F10171. Examples of thromoboxane inhibitors such as (-)-6,8-difluoro-9-p-methylsulfonylbenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid may also be found in US 4,808,608, which is hereby incorporated by reference.

As used herein "COX-2 selective inhibitors" and "thromboxane inhibitors" (including thromboxane synthase inhibitors and thromboxane receptor antagonists) encompass pharmaceutically acceptable salts of the active chemical entity.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-dibenzylethylenediamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When a compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Dosage and Administration

In the present method, the COX-2 selective inhibitor and the thromboxane inhibitor may be administered separately in separate dosage forms or together in a single unit dosage form. Where separate dosage formulations are used, the thromboxane inhibitor and the COX-2 selective inhibitor can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e, sequentially, and in any order. It is preferred that the thromboxane inhibitor and the COX-2 selective inhibitor be co-administered concurrently on a once-a-day dosing schedule; however, varying dosing schedules, such as the thromboxane inhibitor once per day and the COX-2 selective inhibitor once, twice or more times per day, or the COX-2 selective inhibitor once per day and the thromboxane inhibitor once, twice or more times per day, is also encompassed herein. A single oral dosage formulation comprised of both the thromboxane inhibitor and the COX-2 selective inhibitor is preferred. A single dosage formulation will provide convenience for the patient.

The COX-2 selective inhibitor may be administered at a dosage level up to conventional dosage levels for NSAIDs. Suitable dosage levels will depend upon the anti-inflammatory effect of the chosen inhibitor of cyclooxygenase-2, but typically suitable levels will be about 0.001 to 50 mg/kg body weight of the patient per day, preferably 0.005 to 30mg/kg per day, and especially 0.05 to 10mg/kg per day. The compound may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, and especially once per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a COX-2 selective inhibitor per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg of a COX-2 selective inhibitor per kg of body weight per day.

The thromboxane inhibitor may be administered at a dosage level up to conventional dosage levels for thromboxane inhibitors. Suitable dosage levels will depend upon the cardiovascular protective effect of the chosen thromboxane inhibitor, but typically suitable levels will be about 0.001 to 50 mg/kg body weight of the patient per day, preferably 0.005 to 30mg/kg per day, and especially 0.05 to 10mg/kg per day. The compound may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, and especially once per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a thromboxane inhibitor per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for

cytoprotective use from 0.1 mg to about 100 mg of a thromboxane inhibitor per kg of body weight per day.

It will be understood that the dosage of the therapeutic agents will vary with the nature and the severity of the condition to be treated, and with the particular therapeutic agents chosen. The dosage will also vary according to the age, weight, physical condition and response of the individual patient. The selection of the appropriate dosage for the individual patient is within the skills of a clinician.

Pharmaceutical Compositions

Any suitable route of administration may be employed for providing a patient with an effective dosage of drugs of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. However, for the convenience of dosing, the drugs of the present invention are preferably administered orally.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the drugs used in the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, drugs used can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

The instant invention also provides pharmaceutical compositions comprised of a therapeutically effective amount of an COX-2 selective inhibitor in combination with a cardiovascular protective amount of a thromboxane inhibitor, and a pharmaceutically acceptable carrier. One embodiment of the instant compositions is a single unit dosage form adapted for oral administration comprised of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a thromboxane inhibitor and a pharmaceutically acceptable carrier. The active ingredients together with the inert pharmaceutical excipients are made into pharmaceutical unit dosage form such as tablets and capsules using conventioal pharmacy techniques. The combination can also be administered in separate dosage forms, each having one of the active agents. Such separate unit dosage forms may be packaged together into a pharmaceutical product such as blister packs, which are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are

formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

If administered in separate dosage forms, the separate dosage forms are administered such that the beneficial effect of each active agent is realized by the patient at substantially the same time.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

EXAMPLE 1

Tablet Preparation

Tablets containing 25.0, 50.0, and 100.0 mg, respectively, of a thromboxane inhibitor are prepared as illustrated below:

TABLE FOR DOSES CONTAINING
FROM 25-100MG OF THROMBOXANE INHIBITOR

	Amount-mg		
thromboxane inhibitor	25.0	50.0	100.0
Microcrystalline cellulose	37.25	100.0	200.0
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.50	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

EXAMPLE 2

Wet granulated tablet composition

Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

Ingredient	Amount/tablet			
COX-2 Selective Inhibitor	25 mg	12.5 mg	10 mg	5 mg
Microcrystalline cellulose	79.7 mg	86 mg	87.2 mg	89.7 mg
Lactose monohydrate	79.7 mg	86 mg	87.2 mg	89.7 mg
Hydroxypropyl cellulose	6 mg	6 mg	6 mg	6 mg
Croscarmellose sodium	8 mg	8 mg	8 mg	8 mg
Iron oxide	0.6 mg	0.6 mg	0.6 mg	0.6 mg
Magnesium stearate	1 mg	1 mg	1 mg	1 mg

EXAMPLE 3

Directly compressed tablet composition

Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

Ingredient	Amount per tablet			
COX-2 Selective Inhibitor	5 mg	10 mg	12.5 mg	25 mg
Microcrystalline cellulose	45 mg	42.5 mg	113.2 mg	106.9 mg
Lactose anhydrate	45 mg	42.5 mg	113.2 mg	106.9 mg
Croscarmellose sodium	4 mg	4 mg	7.5 mg	7.5 mg
Magnesium stearate	1 mg	1 mg	3.7 mg	3.7 mg

EXAMPLE 4

Hard gelatin capsule composition

Capsule dose strengths of between 1 and 50 mg can be accommodated by varying total fill weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

Ingredient	Amount per capsule
COX-2 Selective Inhibitor	25 mg
Microcrystalline cellulose	37 mg
Lactose anhydrate	37 mg
Magnesium stearate	1 mg
Hard gelatin capsule	1 capsule

EXAMPLE 5

Oral solution

Solution dose strengths of between 1 and 50 mg/5mL can be accommodated by varying the ratio of the two ingredients.

Ingredient	Amount per 5 mL dose
COX-2 Inhibitor	50 mg
	to 5 mL with Polyethylene oxide 400

EXAMPLE 6

Oral suspension

Suspension dose strengths of between 1 and 50 mg/5ml can be accommodated by varying the ratio of the first two ingredients.

Ingredient	Amount per 5 mL dose
COX-2 Selective Inhibitor	101 mg
Polyvinylpyrrolidone	150 mg
Poly oxyethylene sorbitan monolaurate	2.5 mg
Benzoic acid	10 mg
	to 5 mL with sorbitol solution (70%)

EXAMPLE 7

Combination Tablet Preparation

Tablets containing 25.0, 50.0, and 100.0 mg, respectively, of a thromboxane inhibitor and 25 mg COX-2 selective inhibitor are prepared as illustrated below:

	Amount-mg		
Thromboxane Inhibitor	25.0	50.0	100.0
COX-2 Selective Inhibitor	25.0	25.0	25.0
Microcrystalline cellulose	37.25	100.0	175.0
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.50	0.75	1.5

Both active compounds, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of thromboxane inhibitor per tablet, and 25 mg COX-2 selective inhibitor, per tablet.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for the treatment or prophylaxis of COX-2-mediated conditions in patients who are at risk of developing thromboembolic events which comprises administering to said patiens a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor and a cardiovascular protective amount of a thromboxane inhibitor.

2. A method of Claim 1 wherein said COX-2 selective inhibitor and said throm boxane inhibitor are adiminstered orally.

3. A method of Claim 1 wherein said COX-2 mediated condition is osteoarthritis.

4. A method of Claim 1 wherein said COX-2 mediated condition is rheumatoid arthritis.

5. A method of Claim 1 wherein said COX-2 mediated condition is selected from Alzeheimer's disease.

6. A method of Claim 1 wherein said COX-2 mediated condition is transformation of colonic adenoma into colonic adenocarcinoma.

7. A method of Claim 1 wherein said COX-2 selective inhibitor is selected from: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(3-fluorophenyl)-5H-furan-2-one;
5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine;
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;
5(S)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(3,4-difluorophenyl)-5H-furan-2-one;
3-((2-thiazolyl)methoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;
3-propyloxy-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;

3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one;
sodium 2-(4-chlorophenyl)-3-(4-(methylsulfonyl)phenyl)-4-oxo-2-pentenoate;
3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;
3-isopropoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;
5,5-dimethyl-3-(3-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran and
5-Chloro-3-(4-(methylsulfonyl)phenyl)-2-(3-pyridinyl)pyridine.

8. A method of Claim 1 wherein said COX-2 selective inhibitor is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone or 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine.

9. A method of Claim 1 wherein said COX-2 selective inhibitor is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide or 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

10. A method of Claim 1 whrein said thromboxane inhibitor is a thromboxane synthase inhibitor.

11. A method of Claim 1 wherein said thromboxane inhibitor is a thromboxane receptor antagonists.

12. A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor and a cardiovascular protective amount of a thromboxane inhibitor, and a pharmaceutically acceptable carrier in a unit dosage form.

13. A pharamceutical composition of Claim 12 wherein said COX-2 selective inhibitor is selected from the group consisting of:
3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(3-fluorophenyl)-5H-furan-2-one;
5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine;
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;
5(S)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(3,4-difluorophenyl)-5H-furan-2-one;
3-((2-thiazolyl)methoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;
3-propyloxy-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;
3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one;
sodium 2-(4-chlorophenyl)-3-(4-(methylsulfonyl)phenyl)-4-oxo-2-pentenoate;
3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;
3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;
3-isopropoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;
5,5-dimethyl-3-(3-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran and
5-Chloro-3-(4-(methylsulfonyl)phenyl)-2-(3-pyridinyl)pyridine.

14. A pharmaceutical composition of Claim 12 wherein said COX-2 selective inhibitor is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone or 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine.

15. A pharmaceutical composition of Claim 12 wherein said COX-2 selective inhibitor is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide or 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

16. A pharmaceutical product comprising (1) a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor in a first oral unit dosage form, (2) a cardioprotective amount of a thromboxane inhibitor in a second oral unit dosage form, and (3) instructions for concurrent or sequential administration of said pharmaceutical product to a patient in need thereof.

17. Use of a COX-2 selective inhibitor and a thromboxane inhibitor in the manufacture of a medicament for treatment or prophylaxis of COX-2 mediated conditions in patients who are at risk of developing thromboembolic events.

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Published:
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26 September 2002

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WO 01/087343 A3

(54) Title: COMBINATION THERAPY USING COX-2 SELECTIVE INHIBITOR AND THROMBOXANE INHIBITOR AND COMPOSITIONS THEREFOR

(57) Abstract: The present invention provides a method for the treatment or prophylaxis of COX-2 mediated conditions in patients who are at risk of developing thromboembolic events which comprises administering to said patient a therapeutically or prophylactically effective amount of a COX-2 selective inhibitor and a cardiovascular protective amount of a thromboxane inhibitor, as well as compositions therefor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/00683

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00 A61P25/28 A61P19/02 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50033 A (LUNDY KRISTIN MARIE ;RICKETTS ANTHONY PAUL (US); PFIZER (US)) 12 November 1998 (1998-11-12) claims 1,4,11 ---	1,2
X	WO 00 23061 A (DEMOPULOS GREGORY A ;HERZ JEFFREY M (US); PALMER PAMELA P (US); OM) 27 April 2000 (2000-04-27) claims 1,3,14 -----	1,2,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 2002	16/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 01/00683

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-16
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16

Present claims 1-16 relate to compounds and therapeutic applications defined (inter alia) by reference to the following parameters: "COX-2 selective inhibitor", "cardiovascular protective amount of a thromboxane inhibitor" and "COX-2 mediated conditions".
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to combinations of the COX-2 selective inhibitors individually structurally identified by name in the claims and the thromboxane inhibitors individually structurally identified by name on page 16 and 17 of the description, with due regard to the specified therapeutic applications mentioned in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 01/00683

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